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Mutant Genes in High-Risk Childhood Leukemias Identified

Results of collaborative study could lead to development of new diagnostic tools and a new therapeutic target in high-risk disease

(MEMPHIS, Tenn. – May 18, 2009) A research team has pinpointed a new class of gene mutations, which underlie cases of childhood acute lymphoblastic leukemia (ALL) that present high risk of relapse and death. The finding suggests specific drugs that could treat the high-risk leukemia in the children, particularly because such drugs are already in clinical trials for similar blood diseases in adults.

While the cure rate in pediatric ALL has reached about 85 percent, the remaining high-risk cases have proven especially intractable because they arise from different, unidentified genetic mutations.

Discovery of the mutations was led by scientists from St. Jude Children's Research Hospital, the University of New Mexico Cancer Research and Treatment Center, Albuquerque, N.M., and the National Cancer Institute (NCI), part of the National Institutes of Health. This research was done as part of the NCI Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative, which seeks to utilize the study of genomics to identify therapeutic targets in order to develop more effective treatments for childhood cancers. The article appears online May 18 in the early edition of the *Proceedings of the National Academy of Sciences*.

"We have made such great progress in curing children with ALL that the main challenge is now the remaining high-risk patients," said St. Jude Scientific Director, James Downing, M.D., a co-senior author of the study. "We still do not know how to accurately identify them and to effectively treat them to provide the highest chance for a cure. The problem is that within this high-risk group is likely a heterogeneous group of biologic subtypes."

The new study builds on the researchers' previous genetic analysis of high-risk ALL patients' abnormal white blood cells.

"The findings from that analysis hinted that some high-risk ALL cases might arise from mutations in genes that produce enzymes called kinases, which function as biological on-off switches in cells," said Charles Mullighan, M.D., Ph.D., assistant member in St. Jude Pathology and a co-first author of the study. "Such mutations would cause those kinases to be stuck in the on position, triggering the uncontrolled proliferation of white blood cells seen in leukemia."

Thus, the researchers began to analyze the genetic sequences of many kinases known to be components of the proliferation machinery of white blood cells. The team analyzed the blood cells from 187 patients with high-risk ALL. That analysis revealed mutations in about 10 percent of the cases in a type of kinase called JAK, whose members were also known to be mutated in other types of leukemias and related diseases.

"Further studies of these mutant forms of JAKs revealed that the aberrations in their molecular structures could switch them on to drive the blood cell proliferation of ALL," said Stephen Hunger, M.D., chairman of the Children's Oncology Group (COG) ALL committee and a co-senior author of the study. "What's more, in test tube studies, we found that drugs blocking the activation of the mutant JAK kinases prevented uncontrolled growth."

The researchers discovered, in some high-risk ALL patients, that mutations in JAK appeared to work in concert with another mutation—the gene *IKZF1*—which they had earlier found to underlie such cases.

"Our studies of these leukemia subtypes indicate that leukemia is not necessarily a single-cause disease," said Cheryl Willman, M.D., director and CEO of the University of New Mexico Cancer Research and Treatment Center and a co-senior author of the study. "A patient may have multiple different genetic lesions that target different cellular pathways to induce leukemia."

In further studies, the researchers plan to identify mutations in kinase genes and other enzymes that underlie high-risk ALL, as well as explore how these abnormalities might work together to drive the cancers.

The discovery that mutations in JAK underlie some cases of high-risk ALL is enough to warrant clinical trials of inhibitory drugs to treat such cancers.

"JAK-inhibiting drugs are now moving into clinical trials for treatment of such adult myeloproliferative diseases as polycthemia vera, essential thrombocytosis and myelofibrosis," Downing said. "We expect that there will soon be initial clinical studies of the safety and effectiveness of these drugs in children with relapsed ALL in which we have identified JAK mutations."

Such studies would be coordinated by the COG, an international clinical trial cooperative group supported by the NCI.

Other authors of the paper are Racquel Collins-Underwood, Letha A. Phillips, Xiaoping Su, Wei Liu and Brenda Schulman (St. Jude); Sarah Tasian and Mignon Loh (University of California San Francisco); Meenakshi Devidas (Children's Oncology Group); Susan Atlas, I-Ming Chen and Richard C. Harvey (University of New Mexico Cancer Research and Treatment Center, Albuquerque); Robert J. Clifford, Daniela Gerhard, Malcolm Smith and Jinghui Zhang (National Cancer Institute); William Carroll (New York University Cancer Institute); and Gregory H. Reaman (The George Washington University).

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St. Jude Children's Research Hospital

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The Children's Oncology Group/CureSearch

Children's Oncology Group (COG), the world's largest cooperative pediatric cancer research organization, which includes every recognized pediatric cancer program in North America, comprises a network of more than 5,000 physician, nurse, and other clinical and laboratory investigators whose collaboration in clinical and translational research has turned childhood cancer from a virtually incurable disease to one with an overall cure rate approaching 80 percent. COG is committed to conquering childhood cancer through scientific discovery and compassionate care. For more information, please visit www.childrensoncologygroup.org.

The University of New Mexico Cancer Research and Treatment Center

The UNM Cancer Center is New Mexico's only National Cancer Institute-designated cancer center, and is home to the state's largest and most experienced team of cancer experts with 81 board-certified oncology physicians and more than 120 research scientists, supported by more than $50 million in grants annually. As the Official Cancer Center of the State of New Mexico, the Center served 7,600 new patients last year in 84,000 patient visits, treating nearly half of all adults with cancer in the state and virtually all the children.

The National Cancer Institute

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